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# Aromatics from pyrones: esters of terephthalic acid and isophthalic acid from methyl coumalate<sup>†</sup>

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The Diels–Alder reaction of methyl coumalate with alkenes bearing electron-withdrawing groups provides terephthalates or isophthalates in good yields, with the regioselectivity depending on the electron-withdrawing group. The reaction of methyl coumalate with the salt of acrylic acid gave only the monoester of isophthalic acid. Density functional theory (B3LYP/6-31 + G(d,p)) computations of the energies of the competing transition states of the *para*-selective Diels–Alder reactions are in good agreement with experiment. The surprising regioselectivity of methyl coumalate with activated alkenes is attributed to a secondary orbital interaction between the pyrone oxygen and the dienophile LUMO, which switches the regiochemistry expected from simple frontier molecular orbital theory arguments.

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#### Introduction

Terephthalic acid is a commodity chemical produced from petroleum feedstocks.<sup>1</sup> The most common synthesis pathway is the oxidation of *para*-xylene using a cobalt/manganese catalyst in acetic acid. Terephthalic acid and dimethyl terephthalate are employed in the preparation of polyethylene terephthalate (PET), a thermoplastic polymer used in many beverage and food containers and in fabrics. Global production of terephthalic acid was almost fifty million tons.<sup>1</sup> As part of a collaborative effort to produce biorenewable chemicals using enzyme catalysis followed by chemical catalysis,<sup>2</sup> we describe herein an environmentally benign synthesis of esters of isophthalic acid and terephthalic acid and related aromatics from methyl coumalate.

The Diels–Alder reaction of 2-pyrones with alkenes and alkynes has strong literature precedent.<sup>3,4</sup> We recently reported the regioselective Diels–Alder reactions of coumalic acid and methyl coumalate (1) with alpha-olefins,<sup>5</sup> shown in Scheme 1. The reaction involves a Diels–Alder reaction to produce an oxabicyclo[2.2.2]octene intermediate that can be dehydrogenated by a commercial Pd/C catalyst with loss of carbon dioxide to form the *para*-substituted benzoate. This reaction was successful with a variety of alpha-olefins. Oxidation of the alkyl group R in Scheme 1 is known to produce the mono ester of terephthalic acid.<sup>6</sup> This oxidation

step could be avoided if an acrylate or acrylate equivalent could be employed in the cycloaddition step.

The reaction of activated alkenes with methyl coumalate produces bicyclic lactones that are oxidized *in situ* to the aromatic system using Pd/C as a catalyst, as shown in Scheme 2. The use of an activated alkene such as methyl or ethyl acrylate allowed us to conduct the reaction at a much lower temperature than was possible with the unactivated alkenes. Unfortunately, the ratio of 1,4- to 1,3-disubstituted products was only about 3 : 1 in both cases. The yields of these reactions were 25% and 38%, respectively. Previous reports with pyrones by a number of researchers showed a mixture of products when activated alkenes were employed.<sup>7</sup> Raecke and Ogata described reaction conditions to isomerize the potassium salts of phthalic acid and isophthalic acid into terephthalic acid, albeit under harsh conditions.<sup>8,9</sup>

It is clear from Scheme 2 that the two esters are closer in the bicyclic intermediate leading to the *meta*-adduct than they are in the intermediate toward the *para*-adduct. If the steric demand of the ester group was significantly increased, there may be an opportunity to direct the regioselectivity to favor the *para*-diester. Reaction of acrylic acid with diisopropylethylamine generated a salt which was reacted with methyl coumalate at 140 °C. The major product of this reaction was the mono ester of isophthalic acid in 45% yield. The rationale



Scheme 1 Diels-Alder reactions with alkenes.

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Scheme 2 Diels-Alder reaction with activated alkenes. *para*-selectivity was 2.9 : 1.



Scheme 3 Diels-Alder reaction with an amine salt of acrylic acid.

for this intriguing result is not clear; however, it is possible that the Diels–Alder reaction proceeds by way of the exo transition state shown below in Scheme 3 to minimize nonbonded interactions. Attempts to use the salt of coumalic acid were limited by the poor solubility of this compound in organic solvents.

Propiolic acid and its methyl ester were also examined. Use of acetylenic esters had the advantage that the Pd/C catalyst was not needed. The additional double bond in the bicyclic intermediates shown in Scheme 4 enforces the proximity of the two esters in the bicyclic intermediate leading to the *meta*product. Neither compound afforded any regioselectivity. Propiolic acid gave a mixture of products in 64% yield while methyl propiolate yielded 58% of the products. Use of the *tert*butyl ester led to a mixture of products involving loss of the *tert*-butyl group. Since propiolic acid salts have been reported to decompose under thermal conditions,<sup>10</sup> this direction was not pursued.

The reaction of methyl coumalate with acrylonitrile (Scheme 5, X = CN) provided better regioselectivity than the propiolate system, giving the mixture of products in 60% yield with a 1.7 : 1 ratio in favor of the *para*-substituted product. Interestingly, the reaction with acrolein afforded a mixture of adducts in 47% yield with a 4.3 : 1 ratio in favor of the para



Scheme 4 Diels-Alder reactions of propiolates.



Scheme 5 Diels-Alder reactions with acrylonitrile and acrolein.

substitution. The conversion of *para*-formyl benzoates into the terephthalates has been reported by Borhan.<sup>11</sup>

Although we initially explored the influence of steric effects on the partition between *meta-* and *para-*products, it is clear from these experiments that electronic effects also play an influential role. In order to better understand the present results and perhaps later predict the regioselectivity of future experiments, calculations using density functional theory were performed.

#### **Computational methods**

All density functional theory (DFT) calculations were performed using the Gaussian09 software suite<sup>12</sup> employing the B3LYP functional, which consists of the Becke hybrid 3-parameter exchange functional with the correlation functional of Lee, Yang, and Parr.13 The 3-21G basis set was employed to identify the lowest energy product rotamers, and the 6-31 + G(d,p) basis set was used to calculate the geometries and energies of the starting materials, products, and transition states. In all cases for starting materials and products, optimized geometries were found to have zero imaginary frequencies, indicating that the structures represent local minima on the potential energy surfaces. Energy corrections for the zero-point vibrational energy were added unscaled. Transition states for forming these products were located using the Quasi-Newton Synchronous Transit method (QST3). Of note, transition state barriers for related Diels-Alder reactions with this level of theory have been shown to give good agreement with experiment.<sup>14</sup> Computed transition state structures were all found to have one imaginary frequency that connected the starting materials and the product.

The meta or para benzene products can arise from one of two bicyclic intermediate stereoisomers. Additionally, each of the two stereoisomers can exist in several different substituent orientations (rotamers). For example, the Diels–Alder reaction of methyl coumalate with methyl acrylate can lead to two bicyclic stereoisomers, each of which has four different major rotamers. These structures are depicted in Scheme 6. Similar isomers and rotamers were found for the products of the reactions of methyl coumalate with acrolein and acrylonitrile.

The lowest-energy rotamer for each isomer for the carbomethoxy, oxo, and cyano-substituted Diels–Alder products was determined by optimizing each structure at the B3LYP/3-21G level of theory. The lowest energy rotamer for each stereoisomer computed at this level of theory was used as the product for transition state searches. The geometries and energies of the starting materials, product, and transition



Scheme 6 Representation of the different stereoisomers and rotamers for the methyl acrylate Diels–Alder intermediate.

states for each isomer were then computed at the B3LYP/6-31 + G(d,p) level of theory.

#### **Computational results**

The transition states are depicted in Scheme 7. Note that for all of the alkene dienophiles, the lowest energy transition state yields the stereoisomer with the dienophile substituent pointing towards the diene carbons and away from the lactone (*i.e.* top structures in Scheme 6).

Computations suggest nearly degenerate transition states leading to *meta* and *para* bicyclic adducts for the methyl acrylate and acetylenic ester, which would be expected to lead to nearly equal product mixtures (Table 1). This equal product



Scheme 7 Lowest-energy transition states found for formation of the bicyclic products leading to the *para*-substituted benzenes (left) and *meta*-substituted benzene products (right). The two newly-forming bond distances are indicated.

mixture is found experimentally with methyl propiolate, although the methyl acrylate leads to a larger experimental ratio of para over meta (3 : 1). But the transition state leading to the *para* isomer is computed to be lower for the acrylonitrile and acrolein dienophiles by 1.52 and 2.20 kcal mol<sup>-1</sup>, respectively, which would be expected to yield product ratios of ~6 : 1 and 13 : 1 of the *para* product over *meta* product. The trend in the computed ratios are in reasonable agreement with the experimentally observed ratios of 1.7 : 1 and 4.3 : 1 favoring the *para* isomer, respectively.

In explaining the regioselectivity of these reactions, it should be noted that inspection of the transition states shows no evidence of steric effects being important in directing the regiochemistry. Indeed, usually the regioselectivity of Diels-Alder reactions can be predicted using frontier molecular orbital theory by aligning the largest coefficient of the diene HOMO with the largest coefficient of the dienophile LUMO.<sup>15</sup> In more rigorous terms, the orbital interaction energy for the two transition states can be defined as  $2(c_1c_2H_{ij} + c_3c_4H_{ij})^2/$  $(E_{\text{HOMO}} - E_{\text{LUMO}})$  where the *c* terms represent the  $2p_z$  orbital coefficients at the bond-forming carbons, H<sub>ij</sub> represents the resonance integral between these orbitals at the transition state, and  $E_{HOMO}$  and  $E_{LUMO}$  represent the energy of the HOMO and LUMO orbitals, respectively. Thus, this interaction is strongest in transition states where there is a small separation of the HOMO and LUMO and the coefficients on the bonding carbons are large. Usually, only the closest HOMO-LUMO interaction is considered (usually HOMO on the diene and LUMO on the dienophile) while the other interaction (HOMO on dienophile and LUMO on diene) with the larger energy separation is ignored due to its smaller energetic contribution.

However, this simple Frontier Molecular Orbital (FMO) approach for the reactions of methyl coumalate with acrylonitrile, acrolein, and the methyl acrylate, predicts the meta isomer should be favored rather than the para isomer that is favored both computationally and by experiment. As expected based on resonance arguments, the largest HOMO coefficient on the diene  $p_z$  orbitals is on the 1 and 3 carbons, while the largest  $p_z$  LUMO coefficient on the dienophile is on the 6 carbon (see Scheme 8 for numbering). The simplistic picture would suggest that the product would thus favor the bicyclic structure leading to the meta regioisomer. Sometimes, secondary orbital interactions are needed to account for the Diels-Alder regioselectivity.<sup>16</sup> Usually, the secondary interactions considered are between the  $p_z$  orbitals of atoms 8 and 2 for formation of para products and 8 and 3 for formation of meta products; however, adding these terms to the orbital interaction expression above actually leads to a larger predicted preference for the meta isomer over the para isomer. Additionally, including the additional HOMO<sub>dienophile</sub>-LUMO<sub>diene</sub> interaction terms into the above interaction energy expression leads to a prediction that favors the meta isomer over the para isomer.

Thus, some other electronic factor must lead to the regiochemistry observed. We attribute the unexpected regios-

Dienophile	$\Delta\Delta H^{\ddagger} (\text{kcal mol}^{-1})^a$	Computed para-meta ratio <sup>b</sup>	$\Delta H^{\ddagger} para$ (kcal mol <sup>-1</sup> )	$\Delta H^{\ddagger}$ meta (kcal mol <sup>-1</sup> )
CO <sub>2</sub> Me	-0.07	0.9	28.10	28.03
CN	1.52	5.8	29.09	30.60
_СНО 	2.20	12.9	25.50	27.70
CO <sub>2</sub> Me	0.21	1.3	29.53	29.74
$^{a}\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}_{met}$	$_{\rm ta} - \Delta {\rm H}^{\ddagger}_{\rm para}$ . <sup>b</sup> para-meta rati	$o = e^{(\Delta H^{\dagger}_{meta} - \Delta H^{\dagger}_{para})/RT}$ .		

Table 1 Computed transition state energies, differences in transition state energies between meta and para, and the computed ratio of para to meta for the reaction of methyl coumalate with different dienophiles

electivity of the reactions to a different secondary orbital interaction between the pyrone oxygen contribution to the HOMO and the LUMO on the dienophile that favors the transition state leading to the *para* product. This secondary orbital interaction may exert a strong enough influence to invert the natural electronic preference in these reactions to form the *meta* product to favor the *para* product instead. This interaction should favor the *para* isomer over the *meta* isomer because the LUMO on the dienophile substituted with an electron-withdrawing group has a larger coefficient on C6 than on C7 and so this bonding interaction will be stronger in the *para* transition state than in the *meta* transition state.

Several pieces of evidence favor the existence of this secondary orbital interaction. First, inspections of the transition state geometries show that in all cases the bond length between C4 and C6 for the *para* adducts is much shorter than the bond length between C4 and C7 for the *meta* transition state. This much shorter bond length is suggestive of a stronger orbital interaction that could be attributable to the



**Scheme 8**  $p_z$  HOMO orbital coefficients (absolute values, sum of all  $p_z$  orbital coefficients in the basis set) for methyl coumalate and the  $p_z$  LUMO coefficients for electron-withdrawing group substituted dienophiles.

stronger secondary overlap in the *para* transition state. Second, viewing the Kohn–Sham HOMO orbitals of the transition states shows overlap between the oxygen  $p_z$  and the dienophile carbon  $p_z$  orbital (see ESI<sup>†</sup>). Finally, it should be noted that the difference in the coefficients in the LUMO on C6 and C7 is much larger for acrolein than for acrylonitrile and methyl acrylate, which is consistent with this dienophile leading to the largest *para* selectivity.

The reaction of methyl coumalate with a variety of dienophiles has been studied. The relative success using acrolein suggests that electronic factors are more important than steric factors in controlling the regioselectivity in favor of the *para*-substituted product.

#### **Experimental section**

All starting materials were commercially available unless otherwise noted. Methyl coumalate was prepared *via* methylation of coumalic acid.<sup>17</sup> Due to the inherent toxicity of acrolein, the reaction and workup were performed in a wellventilated fume hood. All products were either commercially available or known in the literature. Product ratios were determined by <sup>1</sup>H NMR integration (300 MHz) of purified mixtures of the isomers and comparison to known spectra.

## Methyl coumalate Diels-Alder general procedure (alkenyl dienophiles)

To a solution of methyl coumalate (0.078 g, 0.5 mmol) and 10% Pd/C (0.020 g, 25 wt%) dissolved in toluene in a sealable tube was added alkenyl dienophile (1.5 mmol, 3 equiv.) at rt. The mixture was sealed and stirred for 16 h at the temperature described. The reaction was cooled to rt, opened, filtered through Celite, washing with ethyl acetate, and concentrated *in vacuo* to give the crude product which was purified *via* flash

column chromatography (hexanes : ethyl acetate) to give the desired compounds as inseparable mixtures of *meta* and *para* isomers.

<sup>1</sup>H NMR data was consistent with literature reported values for methyl 3-cyanobenzoate,<sup>18</sup> methyl 4-cyanobenzoate,<sup>19</sup> ethyl methyl isophthalate,<sup>4</sup> ethyl methyl terephthalate,<sup>4</sup> methyl 3-formylbenzoate<sup>20</sup> and methyl 4-formyl benzoate.<sup>21</sup>

## Methyl coumalate Diels-Alder general procedure (alkynyl dienophiles)

To a solution of methyl coumalate (0.078 g, 0.5 mmol) dissolved in toluene in a sealable tube was added alkynyl dienophile (1.5 mmol, 3 equiv.) at rt. The mixture was sealed and stirred for 16 h at the temperature described. The reaction was cooled to rt, opened, filtered through Celite, washing with ethyl acetate, and concentrated *in vacuo* to give the crude product which was purified *via* flash column chromatography (hexanes:ethyl acetate) to give the desired compounds as inseparable mixtures of *meta* and *para* isomers.

<sup>1</sup>H NMR data was consistent with literature reported values for mono-methyl isophthalate,<sup>22</sup> mono-methyl terephthalate,<sup>23</sup> dimethyl isophthalate<sup>24</sup> and dimethyl terephthalate.<sup>25</sup>

#### Mono-methyl isophthalate

To a solution of acrylic acid (0.206 mL, 3 mmol), distilled to remove polymerized material, in toluene (5 mL, 0.2 M) was added *N*,*N*-diisopropylethylamine (0.174 mL, 1 mmol) dropwise at rt. The mixture was stirred for 30 min after which methyl coumalate (0.152 g, 1 mmol) was added, followed by 10% Pd/C (0.038 g, 25%/mass). The reaction was heated to 140 °C for 16 h, then cooled and quenched with sat. aq. NH<sub>4</sub>Cl solution (10 mL). The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine and dried over MgSO<sub>4</sub>. Filtration and concentration *in vacuo* gave the crude product which was purified *via* flash column chromatography (5 : 1–3 : 1 hexanes : EtOAc) to give monomethyl isophthalate in 45% yield as a light yellow solid. The <sup>1</sup>H NMR spectrum was identical to published reports for monomethyl isophthalate.<sup>22</sup>

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